Citation:

Bar-Oz B, Koren G, Nguyen P, Kapur BM. Folate fortification and supplementation: Are we there yet? *Reprod Toxicol*. 2008 Aug; 25 (4): 408-412.

PubMed ID: 18550330

Study Design:

Trend study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the percentage of Ontario women of child-bearing age who exhibit protective levels of RBC folate.

Inclusion Criteria:

- Female
- Child-bearing age (14-45 years old)
- Residing in Ontario, Canada
- Non-anemic (normal hemoglobin female: 120-160g/L)
- Normocytic (MCV: 75-94fL)
- Those who had respective laboratory tests of interest done at the same time (including: RBC and serum folic acid, hemoglobin, mean cell volume and pregnancy test (BHCG).

Exclusion Criteria:

- Females younger than 14 years of age and older than 45 years of age
- Those tested outside of the four general practice or two hospital laboratories in Ontario, Canada
- Those who did not have hemoglobin and MCV results drawn on same date to determine those who were anemic or normocytic.

Description of Study Protocol:

Recruitment

- Laboratory databases from four general practice and two hospitals in the greater Toronto

area were reviewed
- All laboratory samples were anonymous.

Design

Trend study.

Dietary Intake/Dietary Assessment Methodology

Not applicable. Researchers only reviewed laboratory database.

Intervention

Folic acid fortification of flour.

Statistical Analysis

- Chi-square analysis: Used to compare the proportion of women below 900nmol/L among the years in the target population. (900nmol/L has been accepted as the optimal folate concentration needed to minimize the incidence of NTD)
    - P<0.001 for percentage change between 2005 and 2006, 2004 and 2005 and 2002 and 2004
- Mann-Whitney Rank Sum Test: Used to compare medians in RBC folate between the years 2002 and 2006
    - P<0.01 between 2005 and 2006
    - NS between 2002 and 2004 or 2004 and 2005.

Data Collection Summary:

Timing of Measurements

Laboratory values were recorded at one time point per subject for three periods:

- 1995-1997 (pre-fortification)
- 1998 (start of fortification)
- 2000-2006 (post-fortification).

Dependent Variables

RBC folic acid levels.

Independent Variables

Folic acid fortification in flour.

Control Variables

- Child-bearing age
- Hemoglobin and MCV.

Description of Actual Data Sample:

- *Initial N:* 7,997 (total number of women 14 to 45 years old with hemoglobin 120-160g/L and mean cell volume of 75-94fL)
- *Attrition (final N):* Not applicable (data collected at one timepoint per study subject)
- *Age:* 14 to 45 years old
- *Ethnicity:* Not available to researchers
- *Other relevant demographics:* Not applicable
- *Anthropometrics:* None stated
- *Location:* Ontario, Canada.

Summary of Results:

RBC folic acid levels have risen significantly over the years since fortification.

- No significant difference in the medians between 2002-2004
- No significant difference in the medians between 2004-2005
- Significant difference in the medians between 2005-2006.

TABLE: Changes in RBC Folate Over the Years 2002-2006 (Female 14 to 45 years, Hemoglobin 120-160g/L and Mean Cell Volume: 75-94fL)

Year	Number	Mean	Median	5%	95%	Percentage below 900nmol/L
2002	635	1,235 (545)	1,207 (532)	683 (301)	1,887 (832)	16
2004	155	1,015 (477)	928 (409)	556 (245)	1,688 (744)	46.2**
2005	159	972 (428)	910 (401)	522 (230)	1,676 (739)	24.1**
2006	1,537	1,048 (462)	972 (428)*	577 (254)	1,827 (806)	40.7**

* Mann-Whitney Rank Test for medians between 2005 and 2006m P<0.01, NS between 2002 and 2004 or 2004 and 2005

**Chi square, <0.001 for percentage change between the years 2002 and 2004; 2004 and 2005; 2005 and 2006.

- Significant decrease in the population at risk (RBC folate below either 700 or 900nmol/L) (P<0.001) from 1998-2002
- After 2002 this trend reversed with an increase in the proportion of women with levels below 900nmol/L from 24% in 2005 to 40% in 2006
- In a sub-set of 82 pregnant women (plus BHCG test) 36% had RBC folic acid levels below the optimal level of 900nmol/L and 16% were below 700nmol/L.

Author Conclusion:

- Data show that initially folate levels from fortification did indeed substantially improve folate status and the percentage of women at risk
- Furthermore, data suggest that although there was a significant increase in the median RBC folic acid level in 2006 from 2005, there were still 40% of women of child-bearing age who had folic acid levels below 900nmol/L and were exposed to the risk of having babies with NTD
- Goal of optimal prevention of NTD has not yet been achieved and the authors call for urgent action in increasing fortification and supplementation as well as measures to increase awareness and education.

Reviewer Comments:

- *Funding source not given*
- *At-risk population could be explained by:*
  - *Low adherence to peri conceptional folic acid supplements*
  - *Sub-optimal levels of fortification*
  - *"Low-carb" diet wave leading women to decrease consumption of flour-based products.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes

3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???

3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	No
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A

6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	???
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	???

10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	???